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**REMARKS**

Reconsideration of this application in view of the following remarks is respectfully requested.

**I. Status of the claims**

Claims 1-5, 10-11, and 17 are pending in this case. Claims 6-9, 12-16, and 18-24 were canceled in response to the Office Action dated January 10, 2006. Claims 1 and 17 have been amended to replace "tagged protein" with "polyhistidine-tagged cytokine" to provide proper antecedent basis. No new matter has been introduced.

Consideration and entry of this response is respectfully requested. The response places the application into condition for allowance or in better form for consideration on appeal. The response does not introduce any new issue that would require a burdensome search by the Examiner.

**II. Rejections under 35 U.S.C. § 103(a) based on Sporeno in view of Newton**

Claims 1-5, 10-11, and 17 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Sporeno et al. (Cytokine, 6(3):255-264 (1994)) ("Sporeno") in view of Newton et al. (Mol. Biotech. 20:63-76 (2002)) ("Newton"). In response to Applicant's arguments dated September 20, 2006, the Examiner stated that obtaining a product with less contaminants is a clear motivation in the art. Further, the Examiner stated that although Sporeno does not indicate the desirability of further purification, there is no hindsight within the motivation to further purify the composition as the wisdom in the field recognizes the need for purification. Applicants respectfully disagree with the Examiner.

Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case of obviousness. "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." MPEP § 2142 (citing *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991)). The Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness on the basis of Sporeno in view Newton, principally because the Examiner has not established the elements of the *prima facie* case.

Contrary to the Examiner's assertion, the claims are not obvious over Sporeno in view of Newton because one skilled in the art would not be motivated to combine Sporeno and Newton. Sporeno merely relates to purifying Onc M from urea solubilized bacterial cells using a Ni<sup>2+</sup> metal

chelating column. See page 256, second column and page 262, first and second column in Sporeno. Contrary to the Examiner's position, there is no teaching, motivation or suggestion in Sporeno for removing contaminants before the metal chelating step, or that a heparin column is desirable for removing contaminants. Indeed, Sporeno is completely silent with respect to a heparin column. Newton adds nothing that remedies the deficiencies in Sporeno's teachings. Newton merely relates to purification of a non-cytokine protein using heparin and metal chelating columns. Further, Sporeno itself does not provide any motivation to combine the teaching of Newton because Sporeno's methods results in a cytokine preparation that is more than 95% pure and fully active, requiring no further purification. See page 256, first column in Sporeno. Accordingly, one skilled in the art would derive no motivation whatsoever from Sporeno to combine Newton's non-cytokine methods with Sporeno's cytokine methods to arrive at the instant claims for purifying cytokines. One skilled in the art would not be motivated to combine a reference directed to purifying a non-cytokine (Newton) with a reference directed to purifying a cytokine (Sporeno) to arrive at the claims of the instant application directed to purifying cytokines. Thus, the claims cannot be obvious because Sporeno does not provide any motivation with a reasonable expectation of success to modify Sporeno with Newton to arrive at a method for purifying tagged cytokines using heparin and metal chelating columns as recited in the claims.

The Examiner has simply used the Applicant's disclosure and claims as a blueprint because there is no motivation in the cited references to combine the references in the cited manner, and none is actually cited. This is the hindsight trap, wherein pieces of prior art are simply strapped together to match whatever is claimed. It is improper; it violates the law and the Federal Circuit has condemned this approach. Sporeno relates to purifying a cytokine using only a metal chelating column cell but provides no teaching or suggestion that an additional contaminant removal step using a heparin column is desirable or even necessary. Thus, Sporeno fails to teach purifying a cytokine using a heparin column and a metal chelating column. So the Examiner finds a reference that does teach such a heparin column and simply states that if we combine this with Sporeno, voilà, Sporeno's method is now the claimed method.

A §103 rejection based on a combination of references requires a **motivation in the art**, not just a restatement of the beneficial result that was foretold by the Applicant's disclosure and claims. Regarding the Examiner's hindsight approach, the Court of Appeals for the Federal Circuit has said the following:

A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. Close adherence to this methodology is especially important in cases where the very ease with

which the invention can be understood may prompt one "to fall victim to the insidious effect of a hindsight syndrome wherein that which only the invention taught is used against its teacher."

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Most if not all inventions arise from a combination of old elements. Thus, every element of a claimed invention may often be found in the prior art. However, **identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention.** Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant.

*In re Kotzab*, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000) (citations omitted).

Thus, it is respectfully submitted that although the Examiner notes that combining elements to yield the invention would be beneficial, the Examiner does not actually cite any motivation in the art to make that combination, for there exist none indeed. Thus, Applicants respectfully request favorable reconsideration of claims 1-5, 10-11, and 17.

Furthermore, it is only through the Examiner's hindsight that one would combine a cytokine reference with a non-cytokine reference to arrive at the present claims for purifying cytokines, but such hindsight is impermissible. Federal case law has repeatedly explained the importance of the motivation to combine as a safeguard against impermissible hindsight. See *In re Kotzab*, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000) and *DyStar Textilfarben GmbH & Co Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1360 (Fed. Cir. 2006). In fact, *DyStar* further explained that the motivation-to-combine inquiry prevents statutorily proscribed hindsight reasoning when determining obviousness. Moreover, the motivation-to-combine test also informs the Graham analysis for determining obviousness. *Dystar* at 1361.

The Supreme Court in *Graham* set out the factual inquiry which the Patent Office must follow in determining obviousness. *Graham v John Deere Co.*, 383 U.S. 1, 17. The inquiry includes determining the scope and content of the prior art, ascertaining the differences between the prior art and the claims at issue; resolving the level of ordinary skill in the pertinent art, and evaluating evidence of secondary considerations.

#### **Scope and Content of the Cited References**

Sporeno is directed to a method for purifying cytokines using a metal chelating column. However, Sporeno does not describe the use of a metal chelating column together with a heparin column for removing contaminants. In fact, Sporeno does not provide any teaching, motivation or suggestion for removing contaminants before the metal chelating step using a heparin column. Newton adds nothing that remedies the deficiencies in Sporeno because Newton merely relates to

purifying a non-cytokine protein using heparin and metal chelating columns. In addition, Sporeno itself does not provide any kind of motivation to combine the teaching of Newton because Sporeno's methods results in a cytokine preparation that is more than 95% pure and fully active, requiring no further purification. See page 256 of Sporeno.

### **The Differences Between the Cited References and the Claims**

The present claims are directed to a method for purifying polyhistidine-tagged cytokines from a protein preparation, comprising a negatively charged capture support comprises heparin and a tag-specific affinity support. Claims 1 and 17 recite the various steps for the claimed method and claims 2-5 and 10-11 further define additional elements. The present claims differ from Sporeno in that Sporeno does not describe a method for purifying cytokines using heparin and metal chelating columns. Sporeno also does not contemplate additional purification steps of any kind, such as a heparin column or any other column together with a metal chelating column for purifying cytokines. As such, Sporeno does not provide any kind of motivation to combine Newton and arrive at the present claimed method for purifying cytokines using heparin and metal chelating columns.

### **Level of Ordinary Skill in the Pertinent Art**

Both Sporeno and Newton are of at least the level of ordinary skill in the art, yet the claimed invention did not occur to any one of them. Nothing in either Sporeno or Newton provides a motivation to combine the references to arrive at the claims, namely, method for purifying cytokines using heparin and metal chelating columns. One skilled in the art would derive no motivation whatsoever from Sporeno to combine Newton's non-cytokine methods with Sporeno's cytokine methods to arrive at the instant claims for purifying cytokines. Thus, under the Graham analysis, the present claims are nonobvious in view of Sporeno and Newton.

Accordingly, withdrawal of the § 103 rejection of the claims based on Sporeno in view of Newton is in order and is respectfully requested.

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**III. Conclusion**

In light of the above discussion, the Applicants submit that the claims are in allowable condition. A Notice to this effect is respectfully requested.

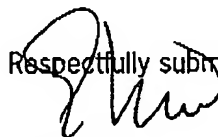
Reconsideration of this application is respectfully requested and a favorable determination is earnestly solicited. The Examiner is invited to contact the undersigned representative if the Examiner believes this would be helpful in expediting the allowance of this application.

Dated: \_\_\_\_\_

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Respectfully submitted,



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